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REMARKS

By the present Communication, claim 67 has been amended and claims 74-80 have been added. Support for the amended claim language may be found in the specification and original claims as filed and do not introduce new matter. The amendment to claim 67 is supported, for example, by claim 24 as filed. Newly added claims 74 and 77 are supported, for example, by Figs. 1 and 5. Newly added claims 75 and 78 are supported, for example, by Example V on page 44, including FIG. 3. Newly added claims 76 and 79 are supported, for example, by page 3, lines 12-14 and page 30, lines 20-26. Newly added claim 80 is supported, for example, by page 30. Upon entry of the present amendment, claims 31 to 37, 39, 40, 51, 52, 54-56, and 58-80 will be pending.

Regarding the Drawings

The Examiner has objected to the drawings, indicating that Applicants' request that the formal drawings submitted with Applicants' amendment mailed July 2, 2003 in continuation US Serial No. 10/035,368 be utilized for the instant application, is defective. Provided herewith are replacement sheets 1-7 containing Figures 1-9. Accordingly, Applicants request withdrawal of the objection to the drawings.

Claim Rejections under 35 USC § 103

The rejection of claims 37, 55, 56, 58, 59, 63, 64, and 70-73 under 35 U.S.C. §103(a) as allegedly obvious over Shalon et al. (WO 95/35505) in view of Schuh et al. (J. Immunological Methods, 152:59 1992) is respectfully traversed. To establish a *prima facie* case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP § 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). Objective evidence or secondary considerations such as unexpected

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results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence. The weight to be accorded to the evidence depends on the individual factual circumstances of each case. MPEP 2141; Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

The Office Action asserts that Shalon et al. teach microarrays with immobilized reagents that include antibodies and antibody fragments. As conceded in the Office Action, Shalon et al. is silent with respect to antibodies whose antigen specificity is unknown. Furthermore, with respect to claims 70-73 Shalon et al. is silent with respect to a microarray comprising a plurality of antibodies that recognize proteins of a first species. The Office Action asserts that the immunological method of Schuh et al. provides the missing teachings of Shalon et al.

Applicants disagree that Shalon et al. in view of Schuh et al. in combination render the claimed invention obvious. There is no reasonable expectation of success to combine a microarray taught by Shalon et al. with Schuh et al.'s alleged teaching of a plurality of immobilized antibodies whose antigen specificity is unknown or Schuh et al.'s alleged teaching of a plurality of immobilized antibodies that recognize antigens of a first species. The method of Schuh et al. requires that antigen bind to an immobilized antibody in a well of a microtiter plate and further requires that bound antigen be eluted from the plate and detected after separation and blotting. There is no teaching in Shalon et al. that antibodies that are immobilized on arrays using the procedure therein retain their ability to specifically bind antigen. In fact, there is no successful experimental demonstration in Shalon et al. that antibodies can be immobilized using the method disclosed therein, since all of the Examples disclose nucleic acid arrays.

In addition to a lack of teaching of immobilizing antibodies that retain their ability to bind antigen, there is no teaching in Shalon et al. that even if a functional antibody could be immobilized, that a bound antigen could be eluted. A skilled artisan would not be motivated to combine the teachings of Schuh and Shalon because in Schuh, detection occurs by Western blot of eluted antigen. An array, as disclosed in Shalon, would not capture sufficient antigen to allow detection on a gel after elution of the antigen; moreover, elution from individual locations of an array surface, as opposed to wells of a microtiter plate, would be at best difficult, and combined with the gel detection methods of Schuh, infeasible. In fact, there is no teaching in Shalon et al. of elution of any biomolecule after immobilization on the microarrays disclosed therein. Finally, there is no teaching in Shalon et al. that even if an antigen could be eluted after binding a bound antibody, that the antigen could be eluted in sufficient quantity to permit detection on a blot after separation by SDS PAGE. The small volumes taught in Shalon et al. (50 nl and preferably 2 pl to 2 nl, Page 16, 7-10) are at most 1/500th the 50 ul volume used in Schuh et al. (page 61, left column last full paragraph), and preferably as taught by Shalon et al. over 1000-fold less than the volumes of Schuh et al.

In addition to the lack of a *prima facie* case for obviousness as discussed above, there are secondary factors that must be considered with respect to the patentability of the present invention. For example, commercial success has been achieved with the microarray of claim 70 and claims dependent therefrom. In fact, numerous companies have commercialized microarrays and/or kits according to these pending claims (For example, antibody arrays and kits available from Clontech, Montain View, California, www.clontech.com, used in protein expression profiling service from rzpd, Berlin Germany, www.rzpd.de, Panorama[®] antibody microarrays and kits, Sigma-Aldrich, www.sigma-aldrich.com, St. Louis, MO, antibody microarray and expression profiling services from Eurogentec, Inc., San Diego, CA, www.eurogentec.com, also see Raybio[®] antibody arrays available from Ray Biotech, Inc. Norcross,GA (www.raybiotech.com), and antibody arrays from Panomics, Inc., Fremont, CA,

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www.panomics.com). This provides evidence not only of commercial success but also of copying by others. Furthermore, the invention meets the long-felt need of providing tools that make it possible to utilize antibodies to analyze protein expression for large numbers of proteins and/or samples simultaneously. Thus, the cited references do not render the claimed invention obvious. Applicants therefore respectfully request that the rejection be removed.

Claims 39-40 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Shalon et al. in view of Schuh et al. and further in view of Ragg and Whitlow. This rejection is respectfully traversed.

As stated above, there is no reasonable expectation of success to combine a microarray taught by Shalon et al. with a labeled lysate as allegedly disclosed in Schuh et al. Ragg and Whitlow relates to single chain antibody fragments, but are silent as to using an antibody microarray in the method of Schuh et al. Accordingly, Ragg and Whitlow do not make up for the deficiency of Shalon et al. and Schuh et al. Thus, Shalon et al., Schuh et al., and Ragg and Whitlow do not, either alone or in combination, render claims 39-40 obvious. Applicants therefore respectfully request that the rejection of claims 39 and 40 under 35 U.S.C. §103(a) be removed.

Claim 65 stands rejected under 35 U.S.C. §103(a) as obvious over Shalon et al. and Schuh et al., further in view of Kohler et al. The rejection is respectfully traversed. As stated above, there is no reasonable expectation of success to combine a microarray taught by Shalon et al. with a labeled lysate as allegedly disclosed in Schuh et al. Kohler et al. relates to using hybridomas to produce antibodies, but is silent as to using an antibody microarray in the method of Schuh et al. Accordingly, Kohler et al. does not make up for the deficiency of Shalon et al. and Schuh et al. Thus, Shalon et al., Schuh et al., and Koehler et al. do not, either alone or in

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combination, render claim 65 obvious. Applicants therefore respectfully request that the rejection of claim 65 under 35 U.S.C. §103(a) be removed.

Claims 31-33, 36, 51, 52, 54, 60-61, and 67-69 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shalon et al. in view of Schuh et al. and further in view of Foster et al. Applicants respectfully traverse this rejection.

Shalon et al. is silent with respect to a kit that includes a first reagent for labeling a cell lysate. As stated above, there is no reasonable expectation of success to combine a microarray taught by Shalon et al. with a cell lysate labeling reagent as allegedly disclosed in Schuh et al. The method of Schuh et al. requires that antigen bind to an immobilized antibody in a well of a microtiter plate and further requires that bound antigen be eluted from the plate and detected after separation and blotting. There is no teaching in Shalon et al. that antibodies that are immobilized on arrays using the procedure therein retain their ability to specifically bind antigen. In fact, there is no successful experimental demonstration in Shalon et al. that antibodies can be immobilized using the method disclosed therein, since all of the Examples disclose nucleic acid arrays.

In addition to a lack of teaching of immobilizing antibodies that retain their ability to bind antigen, there is no teaching in Shalon et al. that even if a functional antibody could be immobilized, that a bound antigen could be eluted. A skilled artisan would not be motivated to combine the teachings of Schuh and Shalon because in Schuh, detection occurs by Western blot of eluted antigen. An array, as disclosed in Shalon, would not capture sufficient antigen to allow detection on a gel after elution of the antigen; moreover, elution from individual locations of an array surface, as opposed to wells of a microtiter plate, would be at best difficult, and combined with the gel detection methods of Schuh, infeasible. In fact, there is no teaching in Shalon et al. of elution of any biomolecule after immobilization on the microarrays disclosed therein. Finally, there is no teaching in Shalon et al. that even if an antigen could be eluted after binding

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a bound antibody, that the antigen could be eluted in sufficient quantity to permit detection on a blot after separation by SDS PAGE. The small volumes taught in Shalon et al. (50 nl and preferably 2 pl to 2 nl, Page 16, 7-10) are at most 1/500th the 50 ul volume used in Schuh et al. (page 61, left column last full paragraph), and preferably as taught by Shalon et al. over 1000-fold less than the volumes of Schuh et al.

In addition to the lack of a *prima facie* case for obviousness as discussed above, there are secondary factors that must be considered with respect to the patentability of the present invention. For example, commercial success has been achieved with the kit of claim 31 and claims dependent therefrom. In fact, numerous companies have commercialized microarrays and/or kits according to the pending claims (For example, antibody arrays and kits available from Clontech, Mountain View, California, www.clontech.com, used in protein expression profiling service from rzpd, Berlin Germany, www.rzpd.de, Panorama[®] antibody microarrays and kits, Sigma-Aldrich, www.sigma-aldrich.com, St. Louis, MO, antibody microarray and expression profiling services from Eurogentec, Inc., San Diego, CA, www.eurogentec.com, also see Raybio[®] antibody arrays available from Ray Biotech, Inc. Norcross, GA (www.raybiotech.com), and antibody arrays from Panomics, Inc., Fremont, CA, www.panomics.com). This provides evidence not only of commercial success but also of copying by others. Furthermore, the invention meets the long-felt need of providing tools that make it possible to utilize antibodies to analyze protein expression for large numbers of proteins and/or samples simultaneously. Thus, the cited references do not render the claimed invention obvious. Applicants therefore respectfully request that the rejection be removed.

Foster et al., relates to enzyme immunoassays and discloses kits, but is silent as to microarrays, reagents for labeling a cell lysate, and using an antibody microarray in the method of Schuh et al. Accordingly, Foster et al. does not make up for the deficiency of Shalon et al. and Schuh et al. The Office Action further asserts with respect to claims 67-69 that Schuh et al. disclose a second reagent for labeling cell lysates. However, the biotin and avidin reagents of

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Schuh et al. are part of one reagent for labeling the same cell lysate. That is, only the NHS-LC biotin reagent labels a cell lysate, wherein the avidin reagent is used to detect the biotin reagent but not to label a second cell lysate. Claim 67 as amended recites that the second reagent is for labeling a second cell lysate. Thus, Shalon et al., Schuh et al., and Foster et al. do not, either alone or in combination, render claims 31-33, 36, 51, 52, 54, 60-61, and 67-69 obvious. Applicants therefore respectfully request that the rejection of these claims under 35 U.S.C. §103(a) be removed.

Claims 34 and 35 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shalon et al., in view of Schuh et al., further in view of Foster et al., and further in view of Ragg and Whitlow. Applicants respectfully traverse this rejection.

As stated above, there is no reasonable expectation of success to combine a microarray taught by Shalon et al. with a labeled lysate as allegedly disclosed in Schuh et al. As indicated above, neither Foster et al., nor Ragg and Whitlow, provide a reasonable expectation of success in using a microarray of Shalon et al. in the method of Schuh et al. Accordingly, Foster et al. and Ragg and Whitlow do not make up for the deficiency of Shalon et al. and Schuh et al. Thus, the references do not render obvious dependent claims 34 and 35 which incorporate the language of claim 31. Applicants therefore respectfully request that the rejection of claims 34 and 35 under 35 U.S.C. §103(a) be removed.

Claim 62 has been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shalon et al., in view of Schuh et al., further in view of Foster et al., and further in view of Kohler et al. Applicants respectfully traverse this rejection.

As stated above, there is no reasonable expectation of success to combine a microarray taught by Shalon et al. with a labeled lysate as allegedly disclosed in Schuh et al. As indicated above, neither Foster et al., nor Kohler et al., provide a reasonable expectation of success in

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using a microarray of Shalon et al. in the method of Schuh et al. Accordingly, Foster et al. and Kohler et al. do not make up for the deficiency of Shalon et al. and Schuh et al. Thus, the references do not render obvious dependent claim 62. Applicants therefore respectfully request that the rejection of claims 62 under 35 U.S.C. §103(a) be removed.

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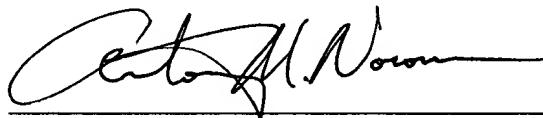
Conclusion

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Enclosed is Check No. 581891 in the total amount of \$1,370.00; which consists of the three-month Petition for Extension of Time fee (\$1,020.00) and the seven (7) additional claims (\$350.00). No other fee is deemed necessary in connection with this submission. However, the Commissioner is hereby authorized to charge any fees required by this submission, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number.

A duplicate copy of this Transmittal Sheet is enclosed.

Respectfully submitted,



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